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### Authors

Greenland, John R  
Michelow, Marilyn D  
Wang, Linlin  
et al.

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# ANESTHESIOLOGY

## COVID-19 Infection

### Implications for Perioperative and Critical Care Physicians

John R. Greenland, M.D., Ph.D., Marilyn D. Michelow, M.D.,  
Linlin Wang, M.D., Ph.D., Martin J. London, M.D.

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In December 2019, a novel pneumonia syndrome was identified in patients clustered around the Huanan Seafood Market in Wuhan, China.<sup>1,2</sup> Next generation sequencing was used to identify a novel coronavirus, now known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in bronchoalveolar lavage fluid from three of these patients. Infection with SARS-CoV-2 leads to the syndrome of Coronavirus Disease 2019 (COVID-19). Rapid international spread of this potentially lethal virus has caused global concern, with 110,000 cases and 3,800 deaths reported to date.<sup>2,3</sup> Here, we will summarize the latest insights into the biology of SARS-CoV-2 and their implications for anesthesiologists in perioperative and intensive care settings.

### COVID-19 Pathogenesis

Relative to the assortment of viruses that cause human upper respiratory tract infection, the group of viruses that cause lower respiratory tract infection is smaller, but includes influenza and parainfluenza, respiratory syncytial virus, cytomegalovirus, and hantavirus. These infections are mostly limited to tracheobronchitis in healthy individuals but can cause severe viral pneumonias in immunocompromised patients. While influenza is one of the best-known causes of pneumonia in the intensive care unit (ICU), this presentation is frequently related to bacterial superinfection, such as with *Staphylococcus aureus*.<sup>4</sup> Some of the rarity of viral pneumonia can be attributed to the types of cells that viruses can infect, termed *tropism*. Thus, while the more common influenza strains (like H1N1) target cells in the trachea and bronchi, influenza pneumonia is particularly linked to avian strains (like H5N1) that skip the upper respiratory epithelium and infect alveolar epithelial cells of the lower respiratory tract.<sup>5</sup>

### ABSTRACT

Healthcare systems worldwide are responding to Coronavirus Disease 2019 (COVID-19), an emerging infectious syndrome caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. Patients with COVID-19 can progress from asymptomatic or mild illness to hypoxemic respiratory failure or multisystem organ failure, necessitating intubation and intensive care management. Healthcare providers, and particularly anesthesiologists, are at the frontline of this epidemic, and they need to be aware of the best available evidence to guide therapeutic management of patients with COVID-19 and to keep themselves safe while doing so. Here, the authors review COVID-19 pathogenesis, presentation, diagnosis, and potential therapeutics, with a focus on management of COVID-19–associated respiratory failure. The authors draw on literature from other viral epidemics, treatment of acute respiratory distress syndrome, and recent publications on COVID-19, as well as guidelines from major health organizations. This review provides a comprehensive summary of the evidence currently available to guide management of critically ill patients with COVID-19.

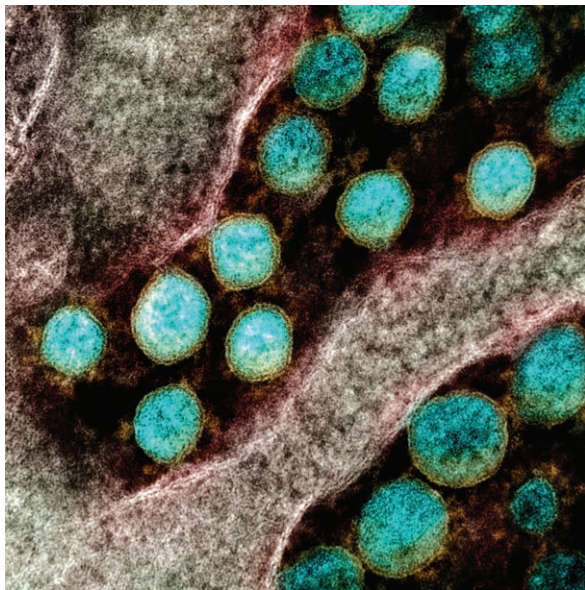
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SARS-CoV-2 is a beta-coronavirus, a family that includes the original severe acute respiratory syndrome (SARS) virus, as well as Middle East respiratory syndrome-related coronavirus (MERS), and endemic human pathogens that are common causes of the cold, including OC43 and HKU1. While beta-coronaviruses have been around for more than 5,000 yr, outbreaks of lethal strains of SARS-CoV in 2002 and Middle East respiratory syndrome-related coronavirus in 2012 have added to their notoriety.<sup>6</sup> SARS-CoV, Middle East respiratory syndrome-related coronavirus, and SARS-CoV-2 all likely originated in bats, with SARS-CoV using civets as intermediary hosts and Middle East respiratory syndrome-related coronavirus passing through camels. Pangolins, also known as scaly anteaters, are implicated in the passage of SARS-CoV-2 to humans on the basis of sequence similarity with pangolin coronaviruses.<sup>7</sup>

The variable clinical manifestations caused by distinct coronavirus strains can be attributed to structural differences in virus proteins, affecting tropism and replication. The “corona” description references the crown-like halo of viral spike (S) proteins observed by electron microscopy (fig. 1). Variations in this S-protein determine which proteins coronaviruses use to enter cells. Early investigations into SARS-CoV-2 suggest that it uses tissue angiotensin converting enzyme-2 as its receptor, a trait shared with SARS, but not Middle East respiratory syndrome-related coronavirus or more common endemic human coronaviruses such as OC43 and HKU1.<sup>8,9</sup> Angiotensin converting enzyme-2

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**Fig. 1.** SARS-CoV-2 virus particles visualized by transmission electron micrograph. Viral particles are shown in blue-green with yellow viral envelope. This image was captured and color-enhanced at the National Institute of Allergy and Infectious Diseases Integrated Research Facility (Fort Detrick, Frederick, Maryland) and used under creative commons license agreement.<sup>107</sup>

is expressed in the lower respiratory tract but not bronchi, as well as enterocytes in the small intestine.<sup>10</sup> Thus, angiotensin converting enzyme-2 dependence may explain the clinical presentations of lower respiratory tract infection and enteritis in COVID-19. Angiotensin converting enzyme-2 expression in vascular endothelium and cardiac myocytes has also been implicated in acute cardiac injury resulting from COVID-19.<sup>11</sup> In animal models, angiotensin converting enzyme inhibitors and angiotensin-receptor blockers increase angiotensin converting enzyme-2 expression and activity, respectively, leading to speculation that these medications could possibly potentiate SARS-CoV-2 infection.<sup>12</sup> Major cardiology societies do not recommend changing renin angiotensin aldosterone system antagonist treatments based on COVID-19 risk at this time.<sup>13</sup> Other sites express angiotensin converting enzyme-2, such as the tongue and parts of the genitourinary tract, but the clinical significance of this finding in COVID-19 is unclear.<sup>14</sup> Binding of S-protein to angiotensin converting enzyme-2 likely contributes directly to pathogenesis, resulting in downregulation of angiotensin converting enzyme-2, increased production of angiotensin II, and resulting increased pulmonary vascular permeability.<sup>15</sup> While SARS-CoV-2-susceptible angiotensin converting enzyme-2 appears universally expressed in humans, there may be genetic variations regulating angiotensin converting enzyme-2 expression that could lead to differential susceptibilities across populations and genotypes.<sup>16</sup>

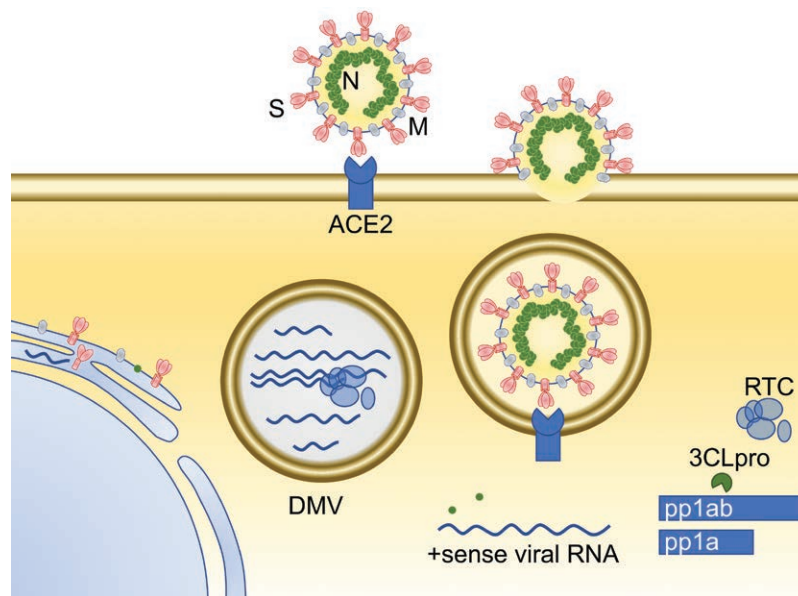
After viral binding to angiotensin converting enzyme-2, the virus may be endocytosed or directly fuse with the cell membrane (fig. 2). A positive-sense viral RNA transcript is then translated by the host cell, yielding two polypeptides. These polypeptides are subsequently divided by viral proteases, yielding the viral replication machinery. Coronaviruses employ multiple mechanisms to shield viral RNA from host detection and subsequent induction of antiviral interferon responses, including direct antagonism of interferon signaling proteins and replication of viral RNA in double membrane vesicles.<sup>15</sup> Nonetheless, COVID-19 strongly induces cytokines and chemokines including interleukin-2, interleukin-4, interleukin-7, interleukin-8, interleukin-10, interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and macrophage inflammatory protein-1- $\alpha$ , suggesting a broad type 1 and type 2 helper T-cell response.<sup>17</sup> It remains uncertain to what extent direct viral cytotoxicity *versus* the host cytokine storm and other immune responses contributes to morbidity in COVID-19.

After initial coronavirus infection, immune responses appear effective in controlling viral infection, suggesting that vaccines should be feasible. There were important caveats from animal vaccine models: antibody responses waned quickly, indicating that immune responses might not be long-lasting.<sup>18</sup> Also, in one mouse coronavirus model of SARS, natural killer cell, antibody, and interferon responses were beneficial, but T-cell responses paradoxically worsened outcomes.<sup>19</sup> Accordingly, vaccines will need to demonstrate safety and effectiveness before widespread adoption.

## COVID-19 Typical Presentation and Diagnosis

The incubation period for SARS-CoV-2 appears to be from 4 to 7 days. Initial reports demonstrated rapid person-to-person viral transmission, with the number of infected individuals doubling every 7.4 days.<sup>20</sup> Viral evolution patterns inferred from viral gene sequence variations suggest that much of the viral transmission that has occurred in the United States has been undiagnosed, where two cases reported 6 weeks apart could potentially represent a cluster of hundreds of infections.<sup>21</sup> Two distinct groups of SARS-CoV-2 sequences have been identified: The L-type represented 96% of the cases in Wuhan, while the more ancestral S-type was found in 38% of cases outside Wuhan. It has been postulated that the S-type could be less severe and thus capable of more rapid spread because of less negative selective pressure.<sup>7</sup>

The majority of patients with COVID-19 infection present with fever as the first symptom. Other common symptoms at onset of illness include cough or fatigue. Less commonly reported symptoms include palpitations, headache, and diarrhea. A subset of patients develop dyspnea at days 5 to 8 after hospitalization. The most commonly reported hematologic laboratory abnormalities with COVID-19 are leukopenia and lymphopenia.<sup>17,22-24</sup> The cause of this leukopenia is not well understood but could relate to bone marrow suppression, lymphocyte sequestration, or apoptosis.<sup>25</sup> The clinical spectrum of COVID-19



**Fig. 2.** Coronavirus biology. Notable coronavirus structural proteins include the spike protein (S), which mediates receptor binding and fusion, the viral membrane protein (M), and the nucleocapsid protein (N). After binding of the viral spike protein to the angiotensin converting enzyme-2 (ACE2) receptor, virions enter cells either by receptor-mediated endocytosis or direct fusion with the cell membrane.<sup>15</sup> Endocytosis is a potential target of chloroquine, which prevents endosomal acidification that triggers viral membrane fusion. Chloroquine may also modify ACE2 terminal glycosylation and inhibit coronavirus binding. Viral RNA is then transcribed to generate polyproteins pp1a and pp1ab that are cleaved by a protease to generate the viral replication machinery. These polyproteins are cleaved to form replication-transcription protein complexes (RTCs) by a viral protease 3-chymotrypsin-like protease (3CLpro). 3CLpro has been postulated to be a target of human immunodeficiency virus protease inhibitors lopinavir or ritonavir, although *in silico* studies have questioned this theory.<sup>108</sup> Viral RNA is replicated and transcribed in double membraned vesicles (DMV) in replication-transcription protein complexes, which include the RNA-dependent RNA polymerase that is the putative target of remdesivir. Viral mRNA is then translated and virions are assembled in the endoplasmic reticulum and golgi.

cases has ranged from asymptomatic to critically ill.<sup>23</sup> While the majority of patients have mild symptoms and good prognosis, up to 15% of patients will develop pneumonia, acute respiratory distress syndrome (ARDS), cardiac injury, renal injury, or multiorgan failure from days 7 to 10 after hospitalization. A subset of patients with COVID-19 will require admission to the ICU and respiratory support with noninvasive or invasive ventilation, or potentially extracorporeal membrane oxygenation.<sup>17,22–24</sup> A summary of COVID-19 symptoms, complications, and treatment in the initial wave of case series publications is presented in table 1.

Of concern to anesthesiologists in the perioperative setting, some patients present with minimal respiratory symptoms. In one of the initial case series, a patient with abdominal symptoms was admitted to a surgical service and infected at least 10 healthcare providers.<sup>24</sup> Abdominal symptoms of COVID-19 may reflect angiotensin converting enzyme-2 expression in the small intestine and are potentially underappreciated, since patients with gastrointestinal symptoms may not be tested for SARS-CoV-2. Indeed, SARS-CoV-2 may be transmitted *via* the fecal-oral route *via* contaminated surfaces.<sup>26</sup>

Pneumonia or abnormalities in chest computed tomography images were detected in almost all hospitalized patients with COVID-19. The characteristic radiographic findings are ground glass opacities, which are typically bilateral and peripheral, coexisting with consolidations or cord-like opacities.<sup>17,27,28</sup> As COVID-19 progresses, “reverse halo” or “crazy-paving” radiologic patterns may become apparent. Notably, some radiologic features are rare with COVID-19, such as lymphadenopathy, nodules, pleural effusions, or cavitation, and would potentially suggest other pathologies.<sup>28</sup>

For diagnosis of SARS-CoV-2, reverse transcriptase-polymerase chain reaction testing is the standard assay. Throat swab and nasal swab samples are commonly used for reverse transcriptase-polymerase chain reaction. While reverse transcriptase-polymerase chain reaction is a useful test to confirm the diagnosis of COVID-19, with limitations of sample collection and kit performance, the total positive rate of reverse transcriptase-polymerase chain reaction for throat swab samples has been reported to be about 30 to 60% at initial presentation.<sup>29</sup> Serial reverse transcriptase-polymerase chain reaction testing and inclusion of lower airway sampling can improve the sensitivity of testing. Commercially



**Table 1.** Published Case Series of COVID-19 Patients

Study Type	No. of Cases	Patient Selection	Location	Primary Presenting Symptoms				Major Complication				Treatment							
				Fever	Cough	Myalgia/ Fatigue	Pneumonia	ARDS	Shock	Kidney Injury	Cardiac Injury	Liver Injury	Secondary Infection	Admitted in ICU	Noninvasive Ventilation	Intubated	ECMO	Death	Reference
Retrospective	1,099	No	30 provinces, China	44%	68%	38%	86%	3%	1%	1%	n/a	n/a	n/a	5%	5%	2%	1%	1%	23
Retrospective	138	Hospitalized	Wuhan, China	99%	82%	96%	100%	20%	9%	4%	17%	n/a	n/a	26%	11%	12%	3%	4%	24
Prospective	41	Hospitalized	Wuhan, China	98%	76%	44%	100%	29%	7%	7%	12%	n/a	10%	32%	24%	5%	5%	15%	17
Retrospective	99	Hospitalized	Wuhan, China	82%	82%	11%	100%	17%	4%	3%	n/a	n/a	5%	23%	13%	4%	3%	11%	22
Retrospective	52	Critically ill	Wuhan, China	98%	77%	12%	100%	67%	n/a	29%	12%	29%	n/a	100%	56%	42%	12%	62%	47
Retrospective	5	Severe	Wuhan, China	100%	100%	60%	100%	80%	20%	20%	n/a	n/a	40%	100%	20%	40%	40%	20%	103
		Pneumonia																	
Retrospective	137	Hospitalized	Hubei province, China	82%	48%	32%	100%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	25%	0%	0%	12%	104
Retrospective	62	Hospitalized	Zhejiang province, China	77%	50%	52%	98%	2%	n/a	n/a	n/a	n/a	n/a	2%	n/a	n/a	0%	0%	105
Retrospective	18	Hospitalized	Singapore	72%	83%	n/a	33%	n/a	n/a	n/a	n/a	n/a	n/a	11%	0%	6%	0%	0%	48

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; n/a, not applicable or not reported.

available molecular tests for endemic coronaviruses, such as the FilmArray Respiratory Panel (BioFire Diagnostics, USA) do not detect SARS-CoV-2 currently. It is expected that SARS-CoV-2 will be added soon.<sup>30</sup> Chest computed tomography may have higher sensitivity for COVID-19 infection, with a sensitivity as high as 97% in one study.<sup>29</sup> Based on challenges with reverse transcriptase-polymerase chain reaction testing, computed tomography imaging has been proposed as a primary tool for COVID-19 detection in hospitalized patients in epidemic areas. However, within the first 2 days after symptom onset, the majority of patients may have normal computed tomography imaging.<sup>28</sup> Thus, early in the disease course, there may be no diagnostic sufficiently sensitive to exclude COVID-19.

Pathology findings of COVID-19 have been reported in some cases.<sup>31,32</sup> While many of the pathologic findings are similar to those seen with coronavirus-associated severe acute respiratory syndrome caused by SARS-CoV and Middle East respiratory syndrome-related coronavirus, such as inflammatory infiltrates and hyaline membrane formation, the findings of inspissated spherical secretions or fibromyxoid exudates are more prominent in COVID-19 infection. Accumulation of these thick secretions likely causes decreased alveolar gas exchange predisposing to respiratory failure, suggesting a potential role for airway clearance and bronchial hygiene in the treatment of COVID-19.

The full ramifications of SARS-CoV-2 infection are yet to be understood. Early work points to a wide variety of psychiatric complications affecting patients, their families and providers, and larger communities relating to anxiety, isolation, frustration, stigma, and guilt.<sup>33</sup> This disease also poses increased risk to specific subpopulations, such as transplant candidates and recipients,<sup>34</sup> and patients with cancer.<sup>35</sup>

## Variation in COVID-19 Presentations

As highlighted in published case series, there is wide variation in clinical presentations of COVID-19, ranging from no symptoms to intractable ARDS and shock. The determinants of these varied outcomes remain unknown, but experience with other viruses suggests that variation in the dose of viral inoculum, route of inoculation, and underlying immune status of the patient can lead to widely variable host responses.<sup>36</sup> Higher viral loads on random sampling identified individuals with greater symptom burden in influenza<sup>37</sup> and greater mortality in adenoviral pneumonia.<sup>38</sup> At the same time, moderate SARS-CoV-2 viral loads can be detected in nasal swabs up to 2 weeks after the onset of symptoms and in asymptomatic individuals.<sup>39</sup> The attributable risk from higher viral inocula is difficult to quantify in real-world settings, but higher viral loads in critically ill patients pose at least a theoretical risk to health-care providers.<sup>40</sup>

The major risk factors for mortality among early reported cases of COVID-19 are old age and underlying

respiratory disease.<sup>24</sup> Again, the reasons for these age associations are unknown, but there are multiple theories that can be extrapolated from host–pathogen biology. For example, immunosenescence could contribute to the increased risk among the aged. As individuals age, the frequency of naive B and T cells diminishes, implying less capacity to recognize and adapt to novel antigens. At the same time, aged immune cells have less proliferative and functional capacity even when responding to known antigens. Such age-related changes in cellular immunity manifest in decreased vaccine effectiveness, worse outcomes in the setting of influenza, respiratory syncytial virus, and herpes zoster infections,<sup>41</sup> and have been demonstrated in mouse models of coronavirus infection.<sup>18</sup> As the lung ages, the airway epithelium restorative capacity is also diminished. Telomere dysfunction is one biologic mechanism of aging, which primarily manifests as pulmonary fibrosis but can also restrict leukocyte proliferation. It is conceivable that poor outcomes from COVID-19 could be linked to short telomeres, as has been reported with pulmonary fibrosis, ARDS, and sepsis.<sup>42,43</sup> It is also possible that younger individuals may have differential susceptibility to SARS-CoV-2. Interestingly, in the rat lung, angiotensin converting enzyme-2 expression decreases with age.<sup>44</sup> Children also could benefit from immunity developed from other coronavirus infections. Indeed, modest cross-reactivity was observed between endemic coronaviruses, such as OC43 and SARS-CoV.<sup>45</sup> This potentially protective cross-reactive immunity would be limited by age and immunosenescence. If fecal–oral transmission resulted in a milder gastroenteritis presentation of SARS-CoV-2, it is also conceivable that children could be subsequently protected from the COVID-19 respiratory syndrome. While we currently can only speculate as to the causes of variation in COVID-19 presentations, these mechanisms likely hold important clues that will inform management and therapeutics.

## Management of COVID-19–associated Respiratory Failure

While most patients with COVID-19 appear to have a relatively mild disease course, a subset will develop hypoxemic respiratory failure with imaging patterns consistent with diffuse viral pneumonitis, organizing pneumonia, or diffuse alveolar damage.<sup>28,46</sup> The true incidence of severe pulmonary disease associated with SARS-CoV-2 is not yet clear, but several studies from Hubei province have reported a 5 to 25% ICU admission rate among hospitalized patients with confirmed SARS-CoV-2, and an ARDS diagnosis in 60 to 70% of patients admitted to the ICU (table 1).<sup>24,47</sup> Among patients who do develop dyspnea and hypoxemia, the median time from onset of symptoms to the development of dyspnea appears to be between 5 and 8 days, with ARDS developing in a smaller subset of those patients at 7 to 10 days.<sup>24,47,48</sup>

The management of severe hypoxemia in COVID-19 is drawn from the management of ARDS and also informed by experience during the 2003 SARS-CoV and 2012 Middle East respiratory syndrome–related coronavirus outbreaks. The World Health Organization has published a practice guideline on the clinical management of COVID-19 severe respiratory infection,<sup>49</sup> and several other groups have also published practice recommendations for the care of patients with COVID-19–associated ARDS.<sup>50–53</sup> The treatment of patients with COVID-19–associated ARDS is made more complex due to necessary infection control interventions such as the use of isolation rooms and the need for care providers to wear appropriate personal protective equipment. Transmission of SARS-CoV-2 from patients to healthcare workers has been reported, and infection control is of primary importance to protect healthcare workers and prevent further spread of SARS-CoV-2.<sup>24,54</sup> The World Health Organization guideline recommends, in addition to routine standard precautions, that providers use droplet and contact precautions when caring for any patients with confirmed or suspected SARS-CoV-2 infection, with the addition of airborne precautions when any aerosol-generating procedure, such as intubation, bronchoscopy, suctioning, or cardiopulmonary resuscitation, is performed.<sup>49</sup> Additional guidelines and frontline reports from groups in Hubei province suggest many providers are utilizing airborne precautions at all times while caring for COVID-19 patients as an additional safety measure.<sup>50,51</sup>

In select patients with COVID-19–associated respiratory failure presenting with hypoxemia that is not adequately treated with low flow nasal cannula oxygen or conventional facemask, a trial of either noninvasive positive pressure ventilation or heated and humidified high flow nasal cannula oxygen may be reasonable before endotracheal intubation and mechanical ventilation.<sup>49</sup> World Health Organization COVID-19 management guidelines, among others, suggest this trial should be of limited duration (1 h) to avoid unrecognized severe respiratory decompensation that requires emergent intervention. The use of high flow nasal cannula or noninvasive positive pressure ventilation is contraindicated in patients with hemodynamic instability, multiorgan failure, or altered mental status.<sup>49,50</sup>

High flow nasal cannula can provide 100% oxygen to patients at a high flow rate, adds a low (2 to 3 cm H<sub>2</sub>O) positive end-expiratory pressure (PEEP) effect, and reduces the work of breathing in patients with acute respiratory failure.<sup>55,56</sup> High flow nasal cannula has been used to treat ARDS with a good safety profile, but given its more recent clinical introduction, there are little data from other outbreaks to guide its use in COVID-19 associated respiratory failure.<sup>49,57</sup> In one study of 310 patients with ARDS randomized to receive initial high flow nasal cannula, noninvasive positive pressure ventilation, or conventional oxygen therapy, the use of high flow nasal cannula did not significantly reduce intubation rates overall, but patients

randomized to the high flow nasal cannula arm had a lower 90-day mortality rate.<sup>58</sup> Patients with moderate or severe ARDS were less likely to require conversion to mechanical ventilation when randomized to the high flow nasal cannula arm of this trial.<sup>58</sup> A systematic review of the use of high flow nasal cannula in ARDS did not find a difference in mortality or intubation rates as compared with usual care, and found that high flow nasal cannula is well tolerated by patients.<sup>57</sup> The use of novel indices, such as the ratio of oxygen saturation/fraction of inspired oxygen to respiratory rate, may be helpful to predict clinical deterioration and the need for intubation when high flow nasal cannula is used.<sup>59</sup>

Given the existing literature base, the use of high flow nasal cannula as an initial strategy for the treatment of COVID-19-associated respiratory failure appears reasonable when patients are closely monitored for worsening respiratory distress. World Health Organization COVID-19 guidelines and others recommend avoiding high flow nasal cannula use in patients with severe or worsening hypercapnia, hemodynamic instability, multiorgan failure, or altered mental status.<sup>49,50</sup>

Although guidelines recommend the use of noninvasive positive pressure ventilation in the management of acute respiratory failure due to cardiogenic pulmonary edema and in patients with chronic obstructive pulmonary disease (COPD) exacerbation leading to respiratory acidosis, no recommendations have been made regarding the use of noninvasive positive pressure ventilation in ARDS.<sup>60</sup> The use of noninvasive positive pressure ventilation in patients with ARDS has been evaluated in several large trials. A recent study reported a high (greater than 40%) rate of noninvasive positive pressure ventilation failure leading to invasive mechanical ventilation in patients with moderate to severe ARDS.<sup>61</sup> In this study, noninvasive positive pressure ventilation failure was associated with increased mortality, as was the use of noninvasive positive pressure ventilation in patients with more severe ARDS ( $\text{PaO}_2/\text{FiO}_2$  less than 150 mmHg).<sup>61</sup> Several authors have suggested that the increased mortality observed when noninvasive positive pressure ventilation is used in patients with more severe ARDS and in those who ultimately require invasive mechanical ventilation may be explained by noninvasive positive pressure ventilation delaying time to a needed intubation, and from lung injury caused by uncontrolled high tidal volumes with noninvasive positive pressure ventilation.<sup>58,60,62</sup> There are limited data to suggest that when noninvasive positive pressure ventilation is delivered *via* helmet to patients with ARDS, failure rates and mortality may be lower than when a conventional noninvasive positive pressure ventilation facemask is used. While a helmet mask may be additionally beneficial from an infection control perspective, this intervention is not widely available.<sup>63</sup>

Experience from the 2009 H1N1 influenza epidemic and the Middle East respiratory syndrome-related coronavirus epidemic also informs the recommendations for use

of noninvasive positive pressure ventilation in COVID-19. A large observational study of H1N1 patients reported a greater than 50% noninvasive positive pressure ventilation failure rate and increased mortality in those patients who failed initial noninvasive positive pressure ventilation and required invasive mechanical ventilation.<sup>64</sup> An observational study of the treatment of patients with Middle East respiratory syndrome-related coronavirus reported a greater than 90% failure rate with the use of noninvasive positive pressure ventilation.<sup>65</sup>

Based on the best available data, the use of noninvasive positive pressure ventilation as an initial strategy for the treatment of COVID-19-associated ARDS is likely reasonable in the subset of patients with mild ARDS, those in whom COPD exacerbation or heart failure may also be contributing to respiratory distress, and when the patient is closely monitored for improvement or worsening respiratory distress.<sup>49,50</sup>

There is substantial concern that using noninvasive positive pressure ventilation or high flow nasal cannula in patients with viral respiratory illness results in increased production of aerosolized virus particles, creating a risk for healthcare workers or contaminating the clinical environment. While multiple studies from the 2003 SARS epidemic have identified participation in tracheal intubation as a risk factor for viral spread to healthcare workers, noninvasive ventilation was only identified as a risk factor in two small studies not considered robust enough to establish the risk of transmission in a 2012 meta-analysis.<sup>66–68</sup> Experimental studies of exhaled air dispersion by mannequins in isolation rooms using conventional low flow nasal cannula, high flow nasal cannula, and continuous positive airway pressure with nasal pillows or full facemask, demonstrated greater exhaled air dispersion with conventional low flow nasal cannula at 5 l/min (up to 1 m from the patient's face) as compared with either high flow nasal cannula or continuous positive airway pressure.<sup>69,70</sup> The authors postulated that lower exhaled air dispersion from high flow nasal cannula or continuous positive airway pressure masks could be related to tighter fit to the face with these modalities, and also that the humidified air generated by these modalities could result in exhalation of larger droplets with a shorter trajectory due to gravity.<sup>70</sup> The use of a full noninvasive positive pressure ventilation facemask might also prevent spread of aerosolized droplets in a patient who is sneezing or coughing.<sup>53</sup> Thus, there is a risk that any method of oxygen delivery to a patient with COVID-19-associated respiratory distress can result in spread of virus-containing exhaled air, especially if the mask is poorly fitted or leaking, but the concern that use of noninvasive positive pressure ventilation or high flow nasal cannula specifically leads to worse environmental contamination is not substantiated by the current available evidence. Patients receiving any supplemental oxygen therapy should be cared for in airborne isolation rooms whenever possible, with staff using full contact, droplet, and airborne isolation

precautions.<sup>51,71</sup> Providers should be aware that coronaviruses can remain infectious on inanimate surfaces for up to 9 days, and all surfaces and equipment used for SARS-2-CoV-infected patients should be carefully disinfected with 70% or greater ethanol for small surfaces or 0.1% or greater sodium hypochlorite for larger surfaces.<sup>72</sup>

Regardless of the choice of initial oxygen therapy for patients with COVID-19-associated respiratory failure, these patients should be closely monitored for deterioration and intubated promptly to avoid the need for an emergent intervention.<sup>51,73</sup> Experience from the 2003 SARS epidemic suggests that intubation is a time when healthcare workers are at high risk for viral transmission from infected patients (odds ratio, 6.6).<sup>66</sup> It should be noted, however, that several of the healthcare providers who contracted SARS while intubating patients were wearing only standard surgical facemasks at the time of intubation, and there is no strong evidence to link intubation with risk of transmission of virus to healthcare workers when proper airborne precautions are taken.<sup>74</sup> Of note, while several *post hoc* reports from the 2003 SARS epidemic and emerging reports from this current epidemic recommend the use of higher level personal protective equipment such as a powered air-purifying respirators, double gloves, coveralls, foot covers, or hoods when performing aerosol generating procedures such as intubation, there does not appear to be evidence to support the superiority of these measures over standard drop-let, contact, and aerosol precautions.<sup>66,73,75</sup> Some have even suggested that the use of increasing layers of barrier precautions without strong evidence to support their application makes patient care more challenging and could increase the risk of contamination during lengthy and complex personal protective equipment removal procedures.<sup>74,75</sup> Application of full barrier precautions has been reported to take at least 5 min, and ideally should not be performed emergently.<sup>74</sup>

When endotracheal intubation is indicated, the World Health Organization COVID-19 clinical guidelines suggest that it be performed by an experienced provider using airborne precautions.<sup>49</sup> The guidelines also recommend the use of any modality (non-rebreather mask, bag valve mask, high flow nasal cannula, or noninvasive positive pressure ventilation) for preoxygenation with 100% oxygen for 5 min, and the use of a rapid sequence induction when possible to avoid coughing or need for positive pressure breaths.<sup>49</sup> Additional guidelines and experiential reports from Hubei province largely echo these recommendations.<sup>50,51</sup> Of note, data from a recent meta-analysis did not note any benefit from the use of high flow nasal cannula for peri-intubation preoxygenation as compared with usual oxygen therapy in patients with hypoxemic respiratory failure.<sup>76</sup> However, high flow nasal cannula may be of benefit to prevent severe hypoxemia during intubations with prolonged apneic times or in patients who have very severe hypoxemia.<sup>76</sup> See table 2 for additional clinical recommendations regarding airway management.

After intubation, management of COVID-19-associated respiratory failure is the same as in ARDS from other causes. U.S., European Union, and recently released United Kingdom ARDS guidelines strongly recommend the use of low tidal volume ventilation (4 to 8 ml/kg predicted body weight in the U.S./European Union guidelines or less than 6 ml/kg in the United Kingdom guidelines, to maintain plateau pressures less than 30 cm H<sub>2</sub>O), with permissive hypercapnia.<sup>77,78</sup> The U.S., European Union, and United Kingdom guidelines also strongly recommend the use of prone positioning for greater than 12 h per day in patients with severe (moderate-severe in United Kingdom guidelines) ARDS, and this recommendation is echoed in the World Health Organization SARS-CoV-2 guideline.<sup>77,78</sup> However, as prone ventilation is a resource-intensive intervention where the endotracheal tube and other lines may become displaced, it is only recommended when there are sufficient human resources and expertise within the medical center for this intervention to be performed safely.<sup>49</sup>

The World Health Organization guidelines for the management of COVID-19 echo the United Kingdom ARDS guidelines in recommending a conservative fluid management strategy for patients without evidence of tissue hypoperfusion.<sup>49,78</sup> While both the U.S./European Union and United Kingdom ARDS guidelines weakly recommend the use of higher PEEP in moderate to severe ARDS and the United Kingdom guidelines weakly recommend the use of neuromuscular blockade by continuous infusion early in moderate to severe ARDS, recent clinical trials challenge these recommendations, and thus, various components of best clinical practice for ARDS remain unclear at this time.<sup>79,80</sup> A large multicenter trial of patients randomized to receive either a conventional low PEEP ventilation strategy or a titrated PEEP strategy resulting in high PEEP combined with lung recruitment maneuvers found increased mortality in the higher PEEP and lung recruitment maneuver arm.<sup>81</sup> Regarding the use of neuromuscular blockade, a recent multicenter randomized trial found no mortality benefit with its use in early moderate to severe ARDS, and more adverse cardiovascular events in the paralysis arm of the study.<sup>82</sup> With these trials in mind, the World Health Organization guidelines suggest cautious use of higher PEEP in moderate or severe ARDS, but not routine use of neuromuscular blockade.<sup>49</sup>

In patients with refractory hypoxemia despite lung protective ventilation with best practices, there are limited data to guide effectiveness of the use of extracorporeal membrane oxygenation. The United Kingdom ARDS guidelines weakly recommend consideration of extracorporeal membrane oxygenation in patients with severe ARDS and refractory hypoxemia, although this recommendation was published before the results of a randomized controlled trial of extracorporeal membrane oxygenation for ARDS, which was stopped early due to lack of a statistically significant mortality benefit between the extracorporeal membrane oxygenation



**Table 2.** Collected Practical Recommendations from Published Literature to Guide Anesthesiologists Caring for Patients with COVID-19

Infection control	<ul style="list-style-type: none"> <li>• Strict adherence to universal precautions at all times.<sup>49</sup></li> <li>• Perform practice drills to familiarize providers with appropriate procedures for donning/doffing personal protective equipment during both nonemergent and emergent situations.</li> </ul>
Intubation	<ul style="list-style-type: none"> <li>• Perform crisis management simulation to help providers prepare for intubation and code blue events in isolation rooms.</li> <li>• Do not delay intubation in patients with worsening respiratory failure, avoid emergent situations where personal protective equipment must be applied in haste.<sup>51,53</sup></li> <li>• For intubations either in the operating room or ICU, wear at least a gown, N95 or higher mask, cap, face shield, and gloves. Some sources suggest powered air-purifying respirators, double gloves, boots, and coveralls.<sup>51,52,71</sup></li> <li>• If using a powered air-purifying respirator, consider an N95 under it to minimize risk of contamination when removing the powered air-purifying respirator.<sup>51</sup></li> <li>• Have a colleague or personal protective equipment champion check proper personal protective equipment application before entering the patient's room or operating room.</li> <li>• Consider writing provider names on gowns or hoods (if worn) to make identification easier.<sup>52</sup></li> <li>• Consider the assembly of intubation kits with all needed supplies in advance, to avoid multiple entries/exits to an isolation room, and delays in obtaining necessary supplies.<sup>51,54</sup></li> <li>• Consider reviewing an intubation plan with all providers before entering the patient room.</li> <li>• Have the minimal number and most experienced personnel in the room whenever possible.<sup>50,51,71,73</sup></li> <li>• Use disposable equipment whenever possible.<sup>73</sup></li> <li>• Preoxygenate for 5 min with 100% oxygen to avoid manual ventilation if possible.<sup>49</sup></li> <li>• When possible, use a rapid sequence or modified rapid sequence induction to avoid bag mask ventilation of the patient.<sup>49</sup></li> <li>• Consider inserting a laryngeal mask airway if prolonged need to mask the patient is anticipated.<sup>71</sup></li> <li>• Rocuronium may be preferred to succinylcholine as paralytic in rapid sequence induction to avoid the potential for paralysis to wear off and the patient to cough if the intubation procedure is prolonged.<sup>71</sup></li> <li>• Attach a high efficiency hydrophobic filter between the mask or endotracheal tube and bag.<sup>51,73</sup></li> <li>• Avoid awake fiberoptic intubation if possible to decrease patient coughing during intubation.<sup>73</sup></li> <li>• Use video laryngoscopy where available to increase the distance between the patient and intubating provider.<sup>51</sup></li> <li>• Put the cuff up immediately after intubation of the trachea.<sup>71</sup></li> <li>• Monitor intubation success with capnography—use of personal protective equipment may make auscultation with a stethoscope difficult or impossible.<sup>51,52,71</sup></li> <li>• Consider the use of ultrasound or chest radiograph to confirm tracheal rather than bronchial intubation, as auscultation may be difficult or impossible.<sup>51</sup></li> <li>• Note that standard 0.05% sodium hypochlorite was not as effective at inactivating coronavirus as 0.1% (double concentration) sodium hypochlorite.<sup>72</sup></li> <li>• Clearly label rooms and hot zones with patients with COVID-19 so that providers know to put on appropriate personal protective equipment.<sup>73</sup></li> <li>• Have a colleague or personal protective equipment champion check proper personal protective equipment removal after exiting the patient's room.</li> </ul>
Oxygen and ventilator management	<ul style="list-style-type: none"> <li>• Use noninvasive positive pressure ventilation, high flow nasal cannula, or mechanical ventilation only in single airborne isolation rooms.<sup>51</sup></li> <li>• Consider having patients on supplementary oxygen via nasal cannula wear a surgical mask over the tubing.<sup>51</sup></li> <li>• Consider the use of in-line suction systems or minimize suctioning if possible.<sup>49</sup></li> <li>• Frequently empty condensation from tubing lines.<sup>53</sup></li> <li>• Consider using medications such as dexmedetomidine, lidocaine, or remifentanyl on extubation to minimize coughing.</li> </ul>
Pre/postoperative care units	<ul style="list-style-type: none"> <li>• Designate an isolated COVID-19 holding/recovery area, ideally a dedicated room with negative pressure ventilation.<sup>51,52</sup></li> <li>• Consider requiring all patients and providers to wear masks in the perioperative setting.<sup>52</sup></li> <li>• Consider having all patients transported to and from operating rooms wear a surgical mask or N95.<sup>52</sup></li> <li>• Consider dedicated hallways and patient transport routes for COVID-19 patients, if possible.<sup>52</sup></li> </ul>
Operating room	<ul style="list-style-type: none"> <li>• Consider a dedicated operating room for patients with COVID-19, ideally with an anteroom and both with negative pressure. If no negative pressure operating rooms, work with engineering to turn off the positive-pressure system.<sup>51</sup></li> <li>• Or, consider using a negative pressure isolation ICU room as an operating room if surgery is necessary on a patient with COVID-19.<sup>106</sup></li> <li>• Use a dedicated anesthesia machine with high efficiency hydrophobic filters on the inspiratory and expiratory limbs of the circuit. Change the filters every 3 to 4 h during operative cases.<sup>52</sup></li> <li>• Consider general anesthesia for patients to reduce the risk of coughing, or if not intubated have patients wear a surgical mask or N95.</li> <li>• Minimize staff and handoffs.</li> <li>• Operating room and ventilator must be completely cleaned after use. Pay special attention to the patient chart, pens, and phones when disinfecting.</li> </ul>
Code blue	<ul style="list-style-type: none"> <li>• Create modular code packs to bring into rooms to prevent contamination of code blue carts and make needed equipment easily accessible in an isolation room during an emergency.<sup>51</sup></li> <li>• Consider implementing a special designation, such as “protected code blue,” to distinguish a code blue in a patient with COVID-19 from other code events.<sup>51</sup></li> <li>• Designated a “protected code blue coach” who makes sure all care providers entering and exiting the room follow safe don/doff procedures with personal protective equipment.<sup>51</sup></li> </ul>
Perioperative clinic	<ul style="list-style-type: none"> <li>• In the case of an epidemic, consider screening preoperative patients for fever, and sending those who are ill or febrile to the emergency room or home as appropriate.</li> <li>• Consider having providers use contact, droplet, and potentially aerosol transmission precautions when seeing patients in the preoperative clinic.</li> </ul>

group and the medical management group.<sup>78,79,83</sup> However, a re-analysis of the data from this trial, as well as a meta-analysis incorporating these new trial data, suggest that extracorporeal membrane oxygenation may provide a mortality benefit in patients with severe ARDS.<sup>84</sup> In a small case-control series during the Middle East respiratory syndrome-related coronavirus outbreak, use of extracorporeal membrane oxygenation for refractory hypoxemia was associated with lower in-hospital mortality.<sup>85</sup> Considering these data, it may be reasonable to refer COVID-19 patients with refractory hypoxemia despite lung protective ventilation for extracorporeal membrane oxygenation in centers with the expertise and resources to properly manage such complex patients.<sup>49,50</sup>

If patients with COVID-19-associated respiratory failure develop superimposed septic shock, adherence to standard sepsis treatment protocols is advised.<sup>49</sup> Additional, nonevidence-based recommendations for the management of COVID-19-associated respiratory failure have been promulgated by a variety of guidelines and published sources, largely focusing on minimizing viral spread to healthcare workers or the environment. These recommendations include minimizing ventilator disconnections, the use of in-line catheters for airway suction,<sup>49</sup> using a high efficiency hydrophobic filter between the patient and the breathing circuit,<sup>51,73</sup> and avoiding the use of nebulized medications in favor of metered dose inhalers if bronchodilators are indicated.<sup>51</sup> A collected list of practical recommendations to guide anesthetic and critical care management of COVID-19 patients is found in table 2. Table 3 provides a list of organizations offering updated guidelines and resources for providers caring for patients with COVID-19.

### Therapeutic Interventions

While there are no drugs specifically approved for treatment of COVID-19, there are multiple ongoing clinical trials and a number of drugs that show promise. SARS-CoV-2 is an RNA virus, like human immunodeficiency virus (HIV) and Ebola, and molecules developed for other RNA viruses may be useful targets (fig. 2). In particular, remdesivir is a nucleotide analog developed for use with Ebola infection. The drug inhibits the RNA-dependent RNA polymerase used

by coronavirions to replicate their genome.<sup>86</sup> Based on *in vitro* evidence of effectiveness, the manufacturer initiated two phase 3 clinical trials of the use of remdesivir in COVID-19 (trial Nos. NCT04292730 and NCT04292899). Similar trials in severe and moderate cases of COVID-19 are underway in China (trial Nos. NCT04252664 and NCT04257656). Remdesivir is also the initial treatment arm in an adaptive clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (trial No. NCT04280705). This adaptive trial will be actively modified to add novel drugs of interest and to replace the control arm with the current best supported regimen. Interestingly, the antimalaria drug chloroquine has also been shown to inhibit SARS-CoV-2 at micromolar concentrations. This agent, which blocks virus infection both at entry and postentry stages, has been used in therapeutic and prophylactic regimens for more than 70 yr, so its safety profile, including prominent neurologic and gastrointestinal side effects, is well known.<sup>87</sup> Among its possible mechanisms of action are altering the pH of endosomes and directly modifying angiotensin converting enzyme-2.<sup>88</sup> Compared with a historical control cohort, SARS-CoV-1 patients treated with combination lopinavir/ritonavir had significantly lower risk of ARDS or death.<sup>89</sup> The combination of lopinavir/ritonavir has been used in COVID-19 cases as well, based on these SARS data and *in vitro* effectiveness.<sup>90,91</sup> However, clinical effectiveness remains unproven, and providers should be cognizant of the known side effect profile for this medication and monitor for hepatotoxicity, hyperglycemia, and arrhythmias.<sup>92</sup> An ongoing clinical trial is comparing patients randomized to lopinavir/ritonavir and the viral fusion inhibitor arbidol (trial No. NCT04252885). As the optimal regimen remains to be determined, affected patients should consider enrolling in clinical trials whenever available.

World Health Organization and Centers for Disease Control and Prevention recommendations<sup>49,93</sup> discourage the use of corticosteroids, given the risk for precipitating infectious and noninfectious complications, such as secondary bacterial infections or hyperglycemia. Further, in Middle East respiratory syndrome-related coronavirus patients, steroid therapy was associated with delayed viral clearance and no improvement in survival.<sup>94</sup> However, it can be difficult to account for the bias that sicker patients are more likely

**Table 3.** Selected Online COVID-19 Resources for Anesthesiologists

American Society of Anesthesiologists	<a href="https://www.asahq.org/about-asa/governance-and-committees/asa-committees/committee-on-occupational-health/coronavirus">https://www.asahq.org/about-asa/governance-and-committees/asa-committees/committee-on-occupational-health/coronavirus</a>
Anesthesia Patient Safety Foundation	<a href="https://www.apsf.org/news-updates/perioperative-considerations-for-the-2019-novel-coronavirus-covid-19/">https://www.apsf.org/news-updates/perioperative-considerations-for-the-2019-novel-coronavirus-covid-19/</a>
Centers for Disease Control and Prevention	<a href="https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html">https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html</a>
Johns Hopkins (live map of global cases)	<a href="https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6">https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6</a>
University of Toronto	<a href="https://www.anesthesia.utoronto.ca/news/coronavirus-and-safety-precautions">https://www.anesthesia.utoronto.ca/news/coronavirus-and-safety-precautions</a>
World Federation of Societies of Anesthesiologists	<a href="https://www.wfsahq.org/resources/coronavirus">https://www.wfsahq.org/resources/coronavirus</a>
World Health Organization	<a href="https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected">https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected</a>

All websites were accessed on March 7, 2020.

to receive steroids. In ARDS, despite multiple randomized controlled studies of corticosteroids, the benefits of corticosteroids remain equivocal.<sup>95</sup> It is likely the benefits are greater for select ARDS patients, such as those early in the disease course or those with superimposed septic shock.<sup>96</sup>

COVID-19 patients have multiple distinct radiologic patterns: diffuse ground glass, reticulation, consolidation suggestive of pneumonitis, diffuse alveolar damage, and organizing pneumonia.<sup>46</sup> In cryptogenic organizing pneumonia, steroid administration has been suggested to prevent progression to hypoxemic respiratory failure in case series.<sup>97</sup> At the same time, the requirement for steroids has been shown to be less relevant for organizing pneumonia with an identified cause, as in COVID-19.<sup>97</sup> Compared with steroids, patients treated with macrolides for mild cryptogenic organizing pneumonia also demonstrated symptom resolution, albeit with higher relapse rates.<sup>98</sup> In case series of COVID-19 patients, steroids and macrolides were commonly used, but we lack data as to their effectiveness.<sup>24,47</sup> In a retrospective analysis, which could be confounded by indication, steroid therapy was associated with decreased risk of death in patients with ARDS and COVID-19.<sup>99</sup> Specific studies in COVID-19 patients are needed to determine whether corticosteroids or macrolides could be beneficial in a subset of patients, such as those with organizing pneumonia patterns.

## Conclusions

In the face of this rapidly emerging global threat, there are several reasons for optimism about future control. As described above, a number of antiviral drugs have shown promise *in vitro*. Even a partially effective antiviral could allow sufficient reduction in viral load so that the immune system can recover and respond to prevent lethal disease. There is even potential that antivirals could be used in chemoprophylaxis to prevent transmission in recently exposed individuals. While resistance to antivirals developed quickly in patients with HIV, studies in coronaviruses suggest this might be less of a problem.<sup>100</sup> Similarly, while HIV readily evades cellular and humoral immunity, sharply limiting vaccination approaches,<sup>101</sup> SARS-CoV infection appeared to induce broad and long-lasting immunity with less evidence of immune escape.<sup>102</sup> Thus, it is likely that as COVID-19 evolves, physicians will have a variety of therapeutic and vaccination options to minimize morbidity and mortality. Until these arrive, anesthesiologists will be called upon to provide supportive care while minimizing the risk of viral transmission to themselves and others.

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## Correspondence

Address correspondence to Dr. Greenland: 4150 Clement Street, Box 111D, San Francisco, California, 94121. john.greenland@ucsf.edu. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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